PATENT SPECIFICATION

DRAWINGS ATTACHED

942,548

Date of Application and filing Complete Specification: March 22, 1960.
No. 10166/60.
Application made in Switzerland (No. 71677) on April 7, 1959.
Application made in Switzerland (No. 75672) on July 13, 1959.
Two Applications made in Switzerland (Nos. 77205 and 77206) on Aug. 21, 1959.
Application made in Switzerland (No. 2049) on Feb. 24, 1960.
(Patent of Addition to No. 911,946 dated Feb. 11, 1959).
Complete Specification Published: Nov. 27, 1963.

942,548

SPECIFICATION NO. 942,548

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of WESTMINSTER BANK LIMITED, of 41, Lothbury, London, E.C.2., a British Company.

THE PATENT OFFICE

COMPLETE SPECIFICATION D 83573/1(9)/R.209 200 10/63 PL

Improvements in or relating to Indole Derivatives Substituted in the 4-Position

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method involving reduction to said amino-containing group, said reduction being
ted under conditions such that the group R_1^1 is not split off. The term "known" indicates a method in actual use or described in the literature on the subject.

It should be noted that the compounds I above consist of the compounds XV above and those derivatives of the compounds XV above in which the protective group on the hydroxy substituent in the 4-position has been split off; this splitting off is effected, according to the invention, in that the end product of the process of the invention is subjected to acid hydrolysis or reduction with hydrogen in the presence of a palladium catalyst or with an alkali metal in liquid ammonia.

[Price 4s. 6d.]

ERRATA

SPECIFICATION No. 942,548

Page 1, heading, *delete* "Class"
Page 2, line 56, *for* "such" *read* "said"
Page 2, line 60, *for* "XVI" *read* "XIV"
Page 3, line 50, *for* "biphenyl" *read* "biphenylyl"
Page 4, line 11, *for* "loyer" *read* "lower"
Page 6, lines 42 and 53, *for* "oxylate" *read* "oxalate"
Page 7, line 53, *after* ")" *insert* a hyphen
Page 7, line 54, *after* "5.8" *insert* "g"
Page 8, lines 3 and 4, *for* "monoethylamide" *read* "monomethylamide"
Page 10, line 39, *for* "mole" *read* "mol."
Page 10, line 48, *after* "Keller's" *insert* "colour"
Page 11, line 47, *after* "dryness" *insert* a full stop

THE PATENT OFFICE
16th March 1964

942,548

PATENT SPECIFICATION

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Complete Specification Published: Nov. 27, 1963.

Index at acceptance:—Class C2, C(1E7E1, 1E7F2, 1E7J, 1E7N5, 2B3A4, 2B3B, 2B3C, 2B3F, 2B3G1, 2B3G3, 2B3G4, 2B3G7, 2B3G8, 2B3G9, 2B9, 2B20, 2B30, 2B48B4, 2B48G3, 3A7V3A4, 3A7V3E1, 3A7V3J4, 3A13C4C, 3A13C10H, 3A2).

International Classification:—C 07 c, d.

COMPLETE SPECIFICATION

Improvements in or relating to Indole Derivatives Substituted in the 4-Position

We, SANDOZ LTD., of Lichtstrasse 35, Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention relates to novel compounds of the indole series, their salts and processes for their manufacture.

The present invention provides indole derivatives having the general formula I shown in the accompanying diagrammatic drawings, wherein R_1 designates a hydrogen atom or an aralkyl group containing from 7 to 10 carbon atoms inclusive, and R_2 designates a hydrogen atom or an alkyl group containing from 1 to 6 carbon atoms inclusive or an aralkyl group containing from 7 to 10 carbon atoms inclusive, each of R_3 and R_4 designates a hydrogen atom or an alkyl group containing from 1 to 6 carbon atoms inclusive, and A designates an alkylene group containing at most 3 carbon atoms, with the proviso that R_1 to R_4 need not be dissimilar, and with the further proviso that A and R_2 together must contain at least 2 carbon atoms when R_3 and R_4 each signify an alkyl group.

The present invention also provides indole derivatives having the general formula XV shown in the accompanying diagrammatic drawings, wherein R_1' designates an aralkyl group containing from 7 to 10 carbon atoms inclusive, and A, R_2, R_3 and R_4 have the above meaning.

The present invention also provides a process for the production of indole derivatives having the general formula XV shown in the accompanying diagrammatic drawings which process is characterized in that an organic radical containing a nitrogen atom and capable of being converted by a method involving reduction into an amino-containing group having the general formula XVI shown in the accompanying diagrammatic drawings wherein A, R_3 and R_4 have the above meaning, is introduced into the 3-position of a compound having the general formula XIII shown in the accompanying diagrammatic drawings, wherein R_1' and R_2 have the above meaning, in known manner for substituting the 3-position of indoles and said organic radical is converted by a method involving reduction to said amino-containing group, said reduction being effected under conditions such that the group R_1' is not split off. The term "known" indicates a method in actual use or described in the literature on the subject.

It should be noted that the compounds I above consist of the compounds XV above and those derivatives of the compounds XV above in which the protective group on the hydroxy substituent in the 4-position has been split off; this splitting off is effected, according to the invention, in that the end product of the process of the invention is subjected to acid hydrolysis or reduction with hydrogen in the presence of a palladium catalyst or with an alkali metal in liquid ammonia.

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For the production of those of the compounds I above which are substituted in the 1-position with an alkyl (C_1 to C_6) or aralkyl (C_7 to C_{10}) group, starting materials may be used which already contain the required substituent. However, it is fully within the scope of the present invention to introduce said substituent in the 1-position (i.e. the radical R_2 = an alkyl group containing 1 to 6 carbon atoms or an aralkyl group) at any stage during the process for producing the compounds I above. It should be noted that all the methods given below for producing the compounds XV above are suitable for producing materials which are unsubstituted in the 1-position.

It should be noted that the use of the benzyl group as a protective grouping for the hydroxy substituent in the 4-position of the starting materials and intermediate compounds is preferred in the process of the invention; however, it is fully within the scope of the present invention to use any alkyl or aralkyl radical as a protective grouping, e.g. a benzhydryl radical, the only condition being that the alkyl or aralkyl group must be capable of being relatively easily split off subsequently; otherwise, however, it will be appreciated that the nature of the protective grouping, e.g. whether it is an alkyl or an aralkyl group or how many carbon atoms it contains, is of no significance as its function is purely that of protecting the hydroxy function in the 4-position.

The process of the present invention may be carried out by a first method which is characterized in that, when it is desired to produce a product wherein R_2 is a hydrogen atom, a compound of the general formula XIV shown in the accompanying diagrammatic drawings wherein R_1' has the above meaning, is reacted with an alkyl magnesium halide to give the corresponding substituted indole magnesium halide, the last mentioned material is reacted with a halogen carboxylic acid halide having the general formula $X_1—CO—A—X_2$ wherein X_1 and X_2 represent each a halogen atom but need not be dissimilar, and A is as defined above, the resulting reaction product is treated with an amine having the general formula XVII shown in the accompanying diagrammatic drawings, wherein R_3 and R_4 have the above significance, and the resulting indolyl(3)-ketone having the general formula II shown in the accompanying diagrammatic drawings is reduced to give a compound of the general formula III shown in the accompanying diagrammatic drawings, said reduction being effected under conditions such that the group R_1' is not split off.

The process of the present invention may be carried out, furthermore, by a second method which is characterized in that the end product of the above process is treated with an alkyl halide containing 1 to 6 carbon atoms or an aralkyl halide in the presence of an alkaline condensation agent so that a 1-substituted indole derivative results.

The process of the present invention may be carried out, furthermore, by a third method which is characterized in that a compound of the general formula XIII shown in the accompanying diagrammatic drawings wherein R_1' and R_2 have the above significance, is converted to the corresponding gramine compound by reaction with formaldehyde and a secondary amine, said gramine is quaternized and treated with an alkali metal cyanide to give an indolyl(3)-acetonitrile of the general formula IV shown in the accompanying diagrammatic drawings, the last mentioned material is saponified by an alkaline treatment to give the corresponding carboxylic acid, the last mentioned material is converted into the corresponding acid halide or azide, said halide or azide is treated with an amine having the general formula XVII defined above, the resulting amide of the general formula V shown in the accompanying diagrammatic drawings wherein R_1', R_2, R_3 and R_4 have the above meaning, is reduced under conditions such that the group R_1' is not split off, to give a compound having the general formula VI shown in the accompanying diagrammatic drawings, wherein R_1', R_2, R_3 and R_4 have the above meaning.

In a modification of the third method above it is possible to proceed in such a way that, when it is desired to produce an end product wherein A represents a methylene group and each of R_3 and R_4 represents a hydrogen atom, the said indolyl(3)-acetonitrile is reduced directly to give a compound having the general formula XVIII shown in the accompanying diagrammatic drawings wherein R_1' and R_2 have the above meaning, such reduction being effected under conditions such that the group R_1' is not split off.

The present invention may also be carried out by a fourth method which is characterized in that, when it is desired to produce an end product wherein R_2, R_3 and R_4 represent each a hydrogen atom, a compound of the general formula XVI defined above is converted by reaction with formaldehyde and a secondary amine to give the corresponding gramine having the general formula VIII shown in the accompanying diagrammatic drawings, wherein R_1' is as defined above, and R designates a dialkylamino group or a radical of a secondary cyclic amine, said gramine is treated with a

nitroalkane of the general formula H—A—NO_2, wherein A is as defined above, in the presence of a proton acceptor, and the resulting nitro compound of the general formula IX shown in the accompanying diagrammatic drawings wherein R_1' and A are as defined above, is reduced to the corresponding amine of the general formula X shown in the accompanying diagrammatic drawings, wherein R_1' and A are as defined above, said reduction being effected under conditions such that the group R_1' is not split off.

The process of the present invention may likewise be carried out by a fifth method which is characterized in that an indolyl(3)-aldehyde having the general formula XI shown in the accompanying diagrammatic drawings, wherein R_1' and R_2 have the above meaning, is heated in the presence of a condensation agent favouring the splitting off of water with a nitroalkane having the formula H—A—NO_2, wherein A has the above significance, the resulting nitro compound having the general formula XII shown in the accompanying diagrammatic drawings wherein R_1' and R_2 have the above meaning and A^1 designates a group A less a hydrogen atom, is reduced to give a basic indole derivative of the general formula VII shown in the accompanying diagrammatic drawings wherein A, R_1' and R_2 have the above meaning, said reduction being effected under conditions such that the group R_1' is not split off.

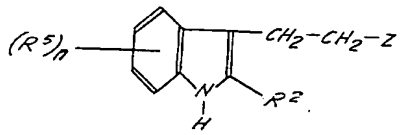
It will be appreciated that the present invention also includes the acid addition salts of the compounds having the general formula I stated above which, in accordance with the invention, may be produced by salifying with an acid. Examples of acids for this purpose are as follows: hydrochloric, hydrobromic, sulphuric, citric, oxalic, tartaric, succinic, maleic, acetic, benzoic, hexahydrobenzoic, methanesulphonic and fumaric.

The compounds of the general formula I above are at room temperature solid, crystalline compounds; in organic solvents most of them are moderately to easily soluble, but in water they are only soluble with difficulty. Their salts with inorganic or organic acids are crystalline at room temperature and most of them are easily soluble in water.

The compounds I above give a positive colour reaction with Keller's reagent (ferric chloride contained in glacial acetic acid and concentrated sulphuric acid). Van Urk's colour reaction (*p*-dimethylaminobenzaldehyde and dilute sulphuric acid) mostly gives a positive result with said compounds I.

The compounds of the general formula I above have interesting pharmacodynamic properties when tested with animals. Examples of such pharmacodynamic properties are stimulation of the central sympathetic nervous system as evidenced by mydriasis, increased blood pressure, increased temperature and blood sugar increase as well as inhibition of intestinal activity. Further such properties are slight calming effect and initiative inhibition, minimising of the sedative and cramp favouring action of reserpine, serotonin antagonism and favouring of spinal reflexes. 4-Hydroxy-3-(2'-dimethylamino-propyl)-indole and 4-hydroxy-3-(3'-dimethylamino-propyl)-indole are specially interesting from the point of view of the minimisation of undesirable side effects of reserpine.

In British Patent Specification No. 781,390 there are mentioned tryptamines having the formula

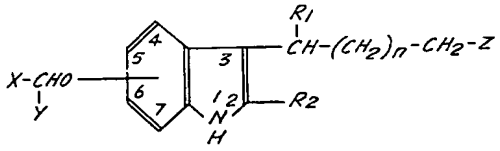


wherein R^2 represents hydrogen; an aryl or substituted aryl radical, e.g. the radicals of the benzene and naphthalene series such as phenyl, naphthyl, lower-alkyl substituted phenyl and naphthyl, wherein lower alkyl contains 1 to 8 carbon atoms inclusive such as tolyl and 2-methylnaphthyl, lower-alkoxy substituted phenyl and naphthyl wherein lower alkoxy contains 1 to 8 carbon atoms inclusive, such as methoxyphenyl and 2 - ethoxy - naphthyl, halogen substituted phenyl and naphthyl such as chlorophenyl, 2-chloro-naphthyl or biphenyl; an aralkyl or substituted aralkyl radical, e.g., benzyl, phenethyl, halobenzyl such as para-chlorobenzyl, alkyl-benzyl such as para-ethylbenzyl, alkoxybenzyl such as para-methoxybenzyl; a lower-alkyl radical containing up to and including eight carbon atoms, e.g., methyl, propyl, or octyl, and R^2 advantageously contains not more than fifteen carbon atoms;

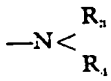
R^5 represents hydroxy, dialkylamino, methylol, aminomethyl, halogen, alkyl, aryl, aralkyl, aryloxy, a fused arylene radical, a benzyloxy radical and a lower alkoxy radical,

n is zero or an integer from one to four and Z represents a primary, secondary or tertiary amino radical.

In said specification there is claimed a process for the preparation of 3-(2-aminoethyl)-indoles and acid addition salts thereof which includes the step of reducing a 3-indoleglyoxylamide or a 3-indoleglycolamide with lithium aluminium hydride. Further, in British Patent Specification No. 744,774 there is described and claimed a process for the preparation of (hydroxy-3-indole)-alkylamines and salts thereof comprising the step of subjecting to hydrogenolysis a (benzyloxy-3-indole)-alkylamine having the formula

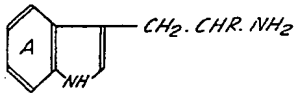


wherein X is phenyl, halophenyl, lower alkoxyphenyl or lower alkylphenyl,
Y is hydrogen, phenyl, halophenyl, loyer alkoxyphenyl or lower alkylphenyl,
R_1 and R_2 are the same or different and represent hydrogen or lower alkyl,
n is zero or one, and
Z represents the amino radical

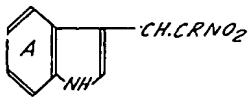


wherein R_3 is hydrogen, alkyl, cycloalkyl, phenyl or aralkyl and
R_4 is alkyl, cycloalkyl, phenyl or aralkyl, and
R_3 and R_4 taken together with the nitrogen also are 5 and 6 atom mono-hetero cyclic amino radicals, and the terms lower alkyl and lower alkoxy refer to radicals containing 1 to 8 carbon atoms inclusive.

Also, in Patent Specification No. 744,773, there is described and claimed a process for the preparation of (benzyloxy-3-indole)-alkylamines and salts thereof, comprising the step of reducing the carbonyl group of a (benzyloxy-3-indole)-alkanoylamide to a methylene group, while in the Patent Specification No. 807, 876 there is described and claimed a process for the manufacture of indole compounds of the formula:



wherein the ring A may optionally be substituted by halogen, alkyl radicals containing not more than 4 carbon atoms, alkoxy radicals containing not more than 4 carbon atoms or aralkoxy radicals and
wherein R stands for hydrogen or for an alkyl radical containing not more than 4 carbon atoms, and the salts thereof, which comprises reducing compounds of the formula:



wherein A and R have the meaning stated above, by means of lithium aluminium hydride as reducing agent.

It will be noticed that the compounds of the present invention all contain a

hydroxy, alkoxy or aralkoxy group in the 4-position of the indole nucleus and it is this feature which gives them the property of stimulating spinal reflexes. None of the compounds of the formula I were known hitherto nor was it known that any significance was attached to the presence of a 4-hydroxy, 4-alkoxy or 4-aralkoxy group in 3-aminoalkyl-indole derivatives.

In the following Examples, which illustrate the invention but in no way limit it, all temperatures are stated in degrees Centigrade; the melting points are uncorrected.

EXAMPLE 1:

4-benzyloxy-3-(2'-dimethylaminopropyl)-indole.

4.8 g of magnesium filings, 14.5 cc (34 g) of methyl iodide and 300 cc of absolute ether are converted into the Grignard salt and subsequently, while stirring at room temperature, a solution of 22.3 g of 4-benzyloxy-indole in 250 cc of absolute ether is added dropwise. Heating to the boil for 1 and a half hours is effected, the material is cooled to 0°, a solution of 25.4 g of α-chloro-propionyl chloride in 200 cc of absolute ether is added dropwise at that temperature and stirring for 30 minutes at 0° and for 2 hours at room temperature is effected. Without isolating the resulting 4-benzyloxy-3-(α-chloro-propionyl)-indole, 150 cc of a 33% alcoholic dimethylamine solution are added at 0° while stirring, the material is left to stand over night and thereafter 250 cc of a 20% ammonium chloride solution is added while cooling. After the entire precipitate has dissolved, the material is shaken out between chloroform and N-tartaric acid solution and the free base which has been obtained from the tartaric acid solution in known manner, is taken up in chloroform. After drying and evaporation of the chloroform, the crude 4 - benzyloxy - 3 - (α - dimethylamino - propionyl) - indole is crystallized from ethyl acetate and then from acetone. The material is present in the form of druses melting at 149—152° after crystallization from acetone.

Keller's colour reaction: blue.

Van Urk's colour reaction: negative.

A solution of 2.27 g of 4-benzyloxy-3-(α-dimethylamino-propionyl)-indole in 140 cc of absolute dioxane is added dropwise to a boiling solution of 2.8 g of lithium aluminium hydride and 60 cc of absolute dioxane and the resulting mixture is heated to the boil for 36 hours. Subsequently decomposition is effected while cooling with ice first with 25 cc of methanol and then with 40 cc of saturated sodium sulphate solution. The precipitate is filtered off with suction, washed with chloroform, the filtrate is evaporated and the crude product is chromatographed on 50 times its weight of aluminium oxide. The required end product is eluted from the column with absolute benzene free from alcohol. The material is recrystallized from benzene/petroleum ether and has a melting point of 126°.

Keller's colour reaction: green.

Van Urk's colour reaction: blue with a violet tinge.

EXAMPLE 2:

4-hydroxy-3-(2'-dimethylamino-propyl)-indole.

First 4-benzyloxy-3-(2'-dimethylamino-propyl)-indole is produced as described in the preceding example. A solution of 480 mg of that material in 40 cc of methanol is shaken with 300 mg of a catalyst containing 5% of palladium on an aluminium oxide carrier in an atmosphere of hydrogen until no more of the last mentioned material is taken up. The catalyst is filtered off with suction, the methanol is distilled off and the residue is crystallized from ethyl acetate; 4-hydroxy-3-(2'-dimethylamino-propyl)-indole forms rhombic plates having a melting point of 138—139°.

Keller's colour reaction: grey blue.

Van Urk's colour reaction: bluish dark green, after standing over night becoming violet.

EXAMPLE 3:

4-benzyloxy-3-(3'-dimethylamino-propyl)-indole.

Using the same method as described in Example 1, starting with 4-benzyloxy-indole and β-chloro-propionyl chloride there is produced 4-benzyloxy-3-(β-chloro-propionyl)-indole and the last mentioned material is converted by reaction with dimethylamine into 4-benzyloxy-3-(β-dimethylamino-propionyl)-indole; the last mentioned material, after recrystallization from acetone, is present in the form of dice having a melting point of 131—132°.

Keller's colour reaction: dark blue.

Van Urk's colour reaction: light blue with a violet tinge.

By reduction with lithium aluminium hydride the required material is obtained which forms prisms and needles having a melting point of 84—86° after recrystallization from benzene/petroleum ether.

Keller's colour reaction: brown green.

Van Urk's colour reaction: blue.

EXAMPLE 4:

4-hydroxy-3-(3'-dimethylamino-propyl)-indole.

First, using the method described in the preceding Example, 4-benzyloxy-3-(3'-dimethylamino-propyl)-indole is produced which is present in the form of prisms and needles having a melting point of 84—86° after recrystallization from benzene/petroleum ether.

662 mg of the last mentioned indole, 400 mg of a catalyst containing 5% of palladium on an aluminium oxide carrier are shaken in 50 cc of methanol with hydrogen until the hydrogen uptake is complete. The catalyst is filtered off with suction, the methanol is distilled off and the residue is recrystallized from methanol/chloroform; the required product has a melting point of 196—199°.

Keller's colour reaction: first dirty green, then blue.

Van Urk's colour reaction: blue violet.

EXAMPLE 5:

1-methyl-3-(2'-dimethylamino-ethyl)-4-benzyloxy-indole.

First 4-benzyloxy-indolyl-magnesium bromide is reacted with the acid chloride of chloracetic acid as described in Example 1 and Example 3, the resulting reaction product is treated with dimethylamine and reduced with lithium aluminium hydride. 3-(2'-dimethylamino-ethyl)-4-benzyloxy-indole crystallizes out from ether/petroleum ether in prisms having a melting point of 119—121°.

Keller's colour reaction: olive brown.

Van Urk's colour reaction: blue.

To a solution of potassium amide in liquid ammonia, produced from 165 mg of potassium, 900 mg of 3-(2'-dimethylamino-ethyl)-4-benzyloxy-indole are added, stirring at −60° is effected for 30 minutes, 650 mg of methyl iodide are added and evaporation of the ammonia is effected after a further 15 minutes. The residue is shaken out between water and chloroform, the chloroform layer is separated and the chloroform evaporated. The resulting crude product is chromatographed on a column of aluminium oxide, 1-methyl-3-(2'-dimethylamino-ethyl)-4-benzyloxy-indole being washed into the filtrate with benzene. Said substance crystallizes from ether/petroleum ether in the form of rodlets having a melting point of 62—67°.

Keller's colour reaction: greenish, then pale brown.

Van Urk's colour reaction: pale brown.

EXAMPLE 6:

1-methyl-3-(2'-dimethylamino-ethyl)-4-hydroxy-indole and its oxylate (1 mol. of acid : 1 mol. of base).

As described in the preceding Example there is first produced 1-methyl-3-(2'-dimethylamino-ethyl)-4-benzyloxy-indole which, after recrystallization from ether/petroleum ether, is present in the form of rodlets having a melting point of 62—67°.

1.92 g of the last mentioned indole are dissolved in 15 cc of methanol and shaken with 500 mg of a palladium catalyst on an aluminium oxide carrier and hydrogen until no more hydrogen is absorbed. Thereupon the catalyst is filtered off and the solvent is evaporated. 1-methyl-3-(2'-dimethylamino-ethyl)-4-hydroxy-indole crystallizes from methanol/ether in the form of irregular plates having a melting point of 125—127°.

Keller's colour reaction: grey.

Van Urk's colour reaction: green.

The oxylate of the last mentioned indole (1 mol. of acid : 1 mol. of base) forms aggregates of needles having a melting point of 166—167° after recrystallization from methanol.

EXAMPLE 7:

1-benzyl-3-(2'-dimethylamino-ethyl)-4-benzyloxy-indole.

To a solution of potassium amide (produced from 1 g of potassium) in liquid ammonia there are added 3.3 g of 3-(2'-dimethylamino-ethyl)-4-benzyloxy-indole, stir-

ring for 30 minutes at −60° is effected, 2.1 g of benzyl bromide are then added and evaporation of the ammonia is effected after a further 30 minutes. The residue is shaken out between water and chloroform, the chloroform phase is dried over sodium sulphate, evaporated and the residue chromatographed on a column of aluminium oxide; the required 1 - benzyl - 3 - (2¹ - dimethylamino - ethyl) - 4 - benzyloxy - indole is washed into the filtrate by means of benzene containing 0.1% of ethanol. The last mentioned indole forms needles having a melting point of 87—88° after recrystallization from benzene/petroleum ether.

Keller's colour reaction: greenish, then becoming pale brown.

Van Urk's colour reaction: brown.

EXAMPLE 8:

1-benzyl-3-(2¹-dimethylamino-ethyl)-4-hydroxy-indole.

As described in the preceding Example there is first produced 1-benzyl-3-(2¹-dimethylamino-ethyl)-4-benzyloxy-indole which forms needles having a melting point of 87—88° after recrystallization from benzene/petroleum ether.

A solution of 2 g of 1-benzyl-3-(2¹-dimethylamino-ethyl)-4-benzyloxy-indole in 30 cc of methanol is shaken with 0.7 g of a palladium catalyst on an aluminium oxide carrier and hydrogen until hydrogen is no longer absorbed, filtration and evaporation of the filtrate to dryness are then effected. The residue is crystallized from benzene giving aggregates of compact prisms. The material, 1 - benzyl - 3 - (2¹ - dimethylamino - ethyl) - 4 - hydroxy - indole, melts at 112—118°.

Keller's colour reaction: olive green.

Van Urk's colour reaction: faint, greenish blue.

EXAMPLE 9:

1-ethyl-3-(2¹-dimethylamino-ethyl)-4-benzyloxy-indole.

5.88 g of 3 - (2¹ - dimethylamino - ethyl) - 4 - benzyloxy - indole are added to a solution of sodium amide in liquid ammonia (produced from 550 mg of sodium) and stirring is effected for a further 45 minutes (approximately) at −60°. A solution of 3.28 g of ethyl iodide in 50 cc of absolute ether is then added and the ammonia is evaporated after a further 3 hours. The residue is dissolved in ether, filtered through talc, the ether evaporated and the residue of the ether solution chromatographed on a column of aluminium oxide by means of benzene. The resulting oily 1 - ethyl - 3 - (2¹ - dimethylamino-ethyl)-4-benzyloxy-indole crystallizes on standing in the form of plates and compact prisms. The melting point of 1-ethyl-3-(2¹-dimethylamino-ethyl)-4-benzyloxy-indole which had solidified from its original oily consistency, is 43—45°.

Keller's colour reaction: brownish.

Van Urk's colour reaction: pale pink.

EXAMPLE 10:

1-ethyl-3-(2¹-dimethylamino-ethyl)-4-hydroxy-indole.

The end product of the last Example is first produced in the manner described therein. The compound consists of an oil which crystallizes on standing as plates and compact prisms having a melting point of 43—45°.

A solution of 3.66 g of the last mentioned indole in 100 cc of methanol is shaken with hydrogen and 3 g of palladium catalyst on an aluminium oxide carrier until the theoretically required amount of hydrogen has been taken up. Filtering is effected, evaporation of the filtrate to dryness and chromatography of the residue on a column of aluminium oxide by means of chloroform are carried out. 1 - ethyl - 3 - (2¹ - dimethylamino - ethyl) - 4 - hydroxy - indole is recrystallized from benzene/petroleum ether in the form of rhombic plates having a melting point of 105—107°.

Keller's colour reaction: dark grey.

Van Urk's colour reaction: emerald green.

EXAMPLE 11:

3-(2¹-methylamino-ethyl)4-benzyloxy-indole

5.8 of 4-benzyloxy-indolyl(3) acetonitrile are boiled at reflux with 12 g of potassium hydroxide in 36 cc of ethanol and 28 cc of water for 15 hours. Thereafter 15 cc of glacial acetic acid and 150 cc of water are added and the precipitated 4-benzyloxy-indolyl(3) acetic acid is filtered off. Upon recrystallization from aqueous methanol the material is present in the form of prisms and plates of a melting point of 186—189°.

1.76 g of 4-benzyloxy-indolyl(3) acetic acid are stirred while cooling with ice with 1.48 g of phosphorus pentachloride in 50 cc of ether until everything has become dis-

solved; thereafter a mixture of 5 cc of methylamine and 10 cc of ether is added dropwise and the resulting material is shaken out between water and chloroform. On evaporation of the chloroform there remains 4-benzyloxy-indolyl(3)-acetic acid monoethylamide which crystallizes from benzene in the form of hexagonal plates having a melting point 150—153°.

To a solution of 1.55 g of 4-benzyloxy-indolyl(3) acetic acid monomethylamide in 40 cc of tetrahydrofuran there is added dropwise a solution of 1.35 g of lithium aluminium hydride in 40 cc of tetrahydrofuran, stirring for 17 hours at a bath temperature of 42° is effected, decomposition with methanol and a saturated sodium sulphate solution is carried out, filtering and shaking out of the filtrate between ether and tartaric acid solution are effected. 3-(2'-methylamino-ethyl)-4-benzyloxy-indole is freed and isolated from the tartaric acid solution; it crystallizes from ether in compact quadrilateral plates having a melting point of 105—106°.

Keller's colour reaction: olive brown.

Van Urk's colour reaction: blue.

EXAMPLE 12:

3-(2'-methylamino-ethyl)-4-hydroxy-indole and its oxalate (2 mol. of base : 1 mol. of acid).

The end product of the preceding Example is first produced in the manner described therein; compact quadrilateral plates having a melting point of 105—106° after recrystallization from ether.

A solution of said indole in 10 cc of methanol is shaken with 150 mg of a palladium catalyst on an aluminium oxide carrier and hydrogen until hydrogen is no longer taken up, filtering is effected, the filtrate is evaporated to dryness and the resulting 3-(2'-methylamino-ethyl)-4-hydroxy-indole, which does not crystallize, is converted into the oxalate (2 mol. of base : 1 mol. of acid) which has a melting point of 150—152°.

Keller's colour reaction: olive green, becoming grey.

Van Urk's colour reaction: blue.

EXAMPLE 13:

3-(2'-ethylamino-ethyl)-4-benzyloxy-indole.

Using the method of Example 11, 4-benzyloxy-indolyl(3) acetonitrile is saponified to give 4-benzyloxy-indolyl(3) acetic acid and the last mentioned material is converted to give 4-benzyloxy-indolyl(3) acetic acid monoethylamide by using monoethylamine instead of monoethylamine as in Example 11. Said amide is recrystallized from benzene in the form of sloping prisms having a melting point of 155—156°.

4-benzyloxy-indolyl(3) acetic acid monoethylamide is reduced thereafter in accordance with Example 11 by means of lithium aluminium hydride to give 3-(2'-ethylamino-ethyl)-4-benzyloxy-indole. The last mentioned material forms needles having a melting point of 97—100° after recrystallization from ether.

Keller's colour reaction: olive brown.

Van Urk's colour reaction: blue.

EXAMPLE 14:

3-(2'-ethylamino-ethyl)-4-hydroxy-indole and its oxalate (2 mol. of base : 1 mol. of acid).

3 - (2' - ethylamino - ethyl) - 4 - benzyloxy - indole is first produced as described in the preceding Example; it is then debenzylated as described in Example 12. It was not possible to crystallize the base.

The oxalate (2 mol. of base : 1 mol. of acid), after recrystallization from methanol/acetone, forms small prisms and plates having a melting point of 218—222°.

Keller's colour reaction: olive green, becoming grey.

Van Urk's colour reaction: blue.

EXAMPLE 15:

1-*n*-butyl-3-(2'-aminoethyl)-4-benzyloxy-indole and its oxalate (1 mol. of base : 1 mol. of acid).

To a suspension of 2.00 g of sodium hydride in 200 cc of toluene there is added a warm solution of 15 g of 4-benzyloxy-indole in a mixture of 75 cc of toluene and 10 cc of dimethyl formamide, the addition being effected while stirring and in an atmosphere of nitrogen. Stirring is effected for 1 and a half hours at room temperature, subsequently 10.5 g of *n*-butyl bromide are added dropwise and the resulting mixture is

kept for 20 hours at 60°. Excess sodium hydride is destroyed by adding methanol, precipitated sodium bromide is filtered off, the filtrate is evaporated and the residue chromatographed with chloroform on a column of aluminium oxide. The resulting oily 1-*n*-butyl-4-benzyloxy-indole solidifies in a refrigerator at + 5°. It has a boiling point of 170—175°/0.1 mm of Hg.

Keller's colour reaction: dark olive green.

Van Urk's colour reaction: red violet.

At 0—10° 29.4 g of a 33% ethanolic dimethylamine solution is added dropwise to a solution of 13.26 g of 1-*n*-butyl-4-benzyloxy-indole in 80 cc of glacial acetic acid and 60 cc of ethanol and then, at 0°, a mixture of 4.4 g of 38% formaldehyde solution and 10 cc of glacial acetic acid is added. The material is left to stand at room temperature for 15 hours, the material is diluted with 1 litre of water, this material is strongly acidified with 1N hydrochloric acid solution and filtration through talc is effected. Subsequently, while cooling, the material is made alkaline with 40% sodium hydroxide solution and extraction with chloroform is effected. The chloroform extracts are dried over sodium carbonate, evaporated and the residue is chromatographed with chloroform on a column of aluminium oxide.

13.74 g of the resulting 1 - *n* - butyl - 4 - benzyloxy - gramine are dissolved in 200 cc of ether and run dropwise into 250 cc of methyl iodide at 0—5°; stirring is effected for 1 hour at that temperature and the material is left to stand in a refrigerator at + 5° for 60 hours. Subsequently the material is evaporated to dryness at 40° in a vacuum and is dried for a further 3 hours at that temperature in a high vacuum. To the resulting 1-*n*-butyl-4-benzyloxy-gramine iodomethylate there are added 18 g of sodium cyanide and 350 cc of water and the resulting mixture is heated for 18 hours while stirring to 80°. Extraction with chloroform is effected, the chloroform solution is dried over sodium carbonate, evaporation is effected and the resulting residue is chromatographed with benzene on a column of aluminium oxide. After recrystallization from benzene/petroleum ether the resulting 1-*n*-butyl-4-benzyloxy-indolyl(3) acetonitrile melts at 67—69°.

Keller's colour reaction: brown.

Van Urk's colour reaction: negative.

A solution of 5.6 g of 1-*n*-butyl-4-benzyloxy-indolyl(3) acetonitrile in 175 cc of ether is added while stirring and in an atmosphere of nitrogen to a boiling solution of 3.4 g of lithium aluminium hydride in 175 cc of ether and the resulting mixture is heated to the boil for 1 and a half hours. Thereafter the resulting complex and excess lithium aluminium hydride are decomposed with methanol and saturated sodium sulphate solution, filtering is effected, the filter paper is washed with ether and the filtrate and washings are extracted with tartaric acid. The acid solution is then made alkaline with dilute sodium hydroxide solution while cooling with ice, extraction by quickly shaking out with ether on several occasions is effected, the united ether extracts are dried over sodium sulphate and the ether is evaporated off. The remaining crude product is chromatographed on a column of aluminium oxide, 1-*n*-butyl-3-(2'-aminoethyl)-4-benzyloxy-indole being eluted into the filtrate with benzene containing 1% of methanol.

4.266 g of the resulting pure indole are dissolved in 20 cc of ethanol and this solution is added to a solution of 1.43 g of oxalic acid in 15 cc of ethanol. The resulting 1 - *n* - butyl - 3 - (2' - aminoethyl) - 4 - benzyloxy - indole oxalate (1 mol. of base : 1 mol. of acid) crystallizes out in the form of druses having a melting point of 180—182°.

Keller's colour reaction: yellow brown.

Van Urk's colour reaction: negative.

EXAMPLE 16:

1-*n*-butyl-3-(2'-aminoethyl)-4-hydroxy-indole
and its oxalate (2 mol. of base : 1 mol. of acid).

6.988 g of 4 - benzyloxy - indolyl(3) acetonitrile, 800 mg of sodium hydride, 80 cc of toluene and 20 cc of dimethyl formamide are heated together for 2 hours while stirring to 60°. After adding 6 g of *n*-butyl bromide the reaction mixture is kept at 60° for a further 15 hours. Excess sodium hydride is decomposed by adding 5 cc of methanol, the reaction mixture is shaken out with 100 cc of water and extraction is effected thrice with chloroform. The united chloroform extracts are dried over sodium carbonate and then evaporated to dryness. The residue is chromatographed with benzene on a column of aluminium oxide. 1-*n*-butyl-4-benzyloxy-indolyl(3) acetonitrile

crystallizes from benzene/petroleum ether and has a melting point of 67—69°.

Keller's colour reaction: brown.

Van Urk's colour reaction: negative.

The conversion of 1-*n*-butyl-4-benzyloxy-indolyl(3) acetonitrile to 1-*n*-butyl-3-(2¹-aminoethyl)-4-benzyloxy-indole is effected according to the same method as described in Example 15. The pure indole is isolated in the form of the oxalate (1 mol. of base : 1 mol. of acid); said oxalate crystallizes from ethanol in the form of druses having a melting point of 180 to 182°.

Keller's colour reaction: yellow brown.

Van Urk's colour reaction: negative.

4.234 g of 1-*n*-butyl-3-(2¹-aminoethyl)-4-benzyloxy-indole oxalate (1 mol of base : 1 mol. of acid) are dissolved in 150 cc of methanol and shaken with hydrogen and 3 g of a palladium catalyst on an aluminium oxide carrier until hydrogen absorption has finished. The catalyst is filtered off and the filtrate is reduced in volume until crystallization commences, 1-*n*-butyl-3-(2¹-aminoethyl)-4-hydroxy-indole oxalate (2 mol. of base : 1 mol. of acid) having a melting point of 271 to 273° crystallizing out from methanol.

Keller's colour reaction: olive green.

Van Urk's colour reaction: light olive green.

EXAMPLE 17:

3-(2¹-aminopropyl)-4-benzyloxy-indole and its methanesulphonate.

0.45 g of sodium are dissolved in 150 cc of nitroethane, 27.5 g of 4-benzyloxy-gramine are added and the material is brought to the boil at reflux for 6 and a half hours in an atmosphere of nitrogen. Filtering is then effected, the filtrate is washed with saturated sodium chloride solution, dried and evaporated to dryness, whereupon the residue is crystallized from chloroform. The resulting 3-(2¹-nitropropyl)-4-benzyloxy-indole forms yellowish, boat-like plates having a melting point of 108—109°.

15.5 g of the last mentioned indole in 400 cc of methanol saturated with ammonia are shaken with Raney nickel prepared from 10 g of Raney alloy, 100 mg of chloroplatinic acid and hydrogen until hydrogen is no longer taken up. The solution is then filtered and the filtrate, which crystallizes spontaneously, is reduced in volume to approximately 100 cc, 3-(2¹-aminopropyl)-4-benzyloxy-indole crystallizing out in small prisms having a melting point of 148—149°.

Keller's colour reaction: olive brown.

Van Urk's colour reaction: blue.

The methane sulphonate of the last mentioned indole crystallizes from ethanol giving needles having a melting point of 271—273°.

EXAMPLE 18:

3-(2¹-aminopropyl)-4-hydroxy-indole and its maleate (1 mol. of base : 1 mole of acid).

3 - (2¹ - aminopropyl) - 4 - benzyloxy - indole is first produced as described in the preceding Example.

A solution of 1.9 g of 3-(2¹-aminopropyl)-4-benzyloxy-indole in 25 cc of methanol are shaken with 1 g of a palladium catalyst on an aluminium oxide carrier with hydrogen until hydrogen absorption has ceased. The solution is then filtered, the filtrate is evaporated to dryness and the residue is crystallized from a mixture of chloroform with methanol and petroleum ether, 3-(2¹-aminopropyl)-4-hydroxy-indole crystallizing out in the form of indefinite crystals having a melting point of 125—126°.

Keller's reaction: green, becoming grey.

Van Urk's colour reaction: dull blue.

The maleate (1 mol. of the last mentioned base : 1 mol. of acid) forms prisms having a melting point of 174—175° on recrystallizing from acetone.

EXAMPLE 19:

1-methyl-3-(2¹-aminopropyl)-4-benzyloxy-indole.

2.2 g of sodium are dissolved in 500 cc of liquid ammonia, oxidation is effected by adding a trace of ferric nitrate to give sodium amide and 10 g of 4-benzyloxy-indole are added. After 15 minutes the resulting dark brown solution is mixed with a mixture of 18 g of methyl iodide and 10 cc of absolute ether and after a further 15 minutes the ammonia is evaporated. The dry residue is shaken between water and ether and the ether solution is reduced in volume to a considerable extent; thereafter petroleum ether

is added very carefully, whereupon 1-methyl-4-benzyloxy-indole crystallizes out in the form of octahedra having a melting point of 78—79°.

With the exclusion of moisture 18 cc of dimethyl formamide and 5 cc of phosphorus oxychloride are mixed at 10—20°. Subsequently over a period of 30 minutes at 20—30° a solution of 11.6 g of 1-methyl-4-benzyloxy-indole in 12.5 cc of dimethyl formamide is added, heating for 45 minutes to 35—37° is effected and the reaction mixture is added while stirring to 50 g of ice and 50 cc of ice water. Thereafter a solution of 9.5 g of solid sodium hydroxide in 50 cc of water is added during 30 minutes at 20—30° in such a way that three quarters of the solution is added slowly and dropwise and the last quarter is added at once. Dilution with 100 cc of water is effected, boiling for 3 minutes and cooling. The precipitated 1-methyl-4-benzyloxy-indole-3-aldehyde is filtered off with suction, washed five times with a total of 25 cc of water and dried at 80° in a vacuum. 1-methyl-4-benzyloxy-indole-3-aldehyde crystallizes from chloroform/petroleum ether in the form of needles having a melting point of 120°.

Keller's and Van Urk's colour reactions: negative.

13 g of 1 - methyl - 4 - benzyloxy - indole - 3 - aldehyde, 2.85 g of ammonium acetate and 70 cc of nitroethane are heated to 102° for 40 minutes while stirring, the reaction mixture is then cooled and added to 200 cc of water. The 1 - methyl - 3 - (2¹ - methyl - 2¹ - nitrovinyl) - 4 - benzyloxy - indole which has crystallized, is filtered with suction and washed 6 times with a total of 100 cc of water. 1-methyl-3-(2¹-methyl-2¹-nitrovinyl)-4-benzyloxy-indole crystallizes from chloroform/ethanol in the form of needles having a melting point of 142°.

Keller's colour reaction: first dark red, immediately becoming brown.

Van Urk's colour reaction: yellowish.

A solution of 13.85 g of 1-methyl-3-(2¹-methyl-2¹-nitrovinyl)-4-benzyloxy-indole in 130 cc of tetrahydrofuran is added dropwise to a solution heated to 50° of 21 g of lithium aluminium hydride in 250 cc of tetrahydrofuran, the addition being effected over a period of 15 minutes, and stirring at 50° is effected for 10 hours. Thereafter the complex and excess of lithium aluminium hydride are decomposed with methanol and saturated sodium sulphate solution, filtering is effected, the residue on the filter paper is washed with chloroform and evaporation of the filtrate to dryness is effected. The residue is shaken out between ether and tartaric acid, the acid solution is made alkaline with dilute sodium hydroxide solution while cooling with ice, extraction with several portions of ether is quickly effected, the united ethereal extracts are dried over sodium sulphate and the ether is evaporated off. 1-methyl-3-(2¹-aminopropyl)-4-benzyloxy-indole crystallizes from ethyl acetate in the form of needles having a melting point of 109—110°.

Keller's colour reaction: olive green.

Van Urk's colour reaction: negative.

EXAMPLE 20:

1-methyl-3-(2¹-aminopropyl)-4-hydroxy-indole.

First 1-methyl-3-(2¹-aminopropyl)-4-benzyloxy-indole is produced as in the preceding Example.

A solution of 3.987 g of the last mentioned indole in 50 cc of methanol is shaken with hydrogen in the presence of 2.5 g of a palladium catalyst on an aluminium oxide carrier until hydrogen is no longer taken up and the filtrate is evaporated to dryness The residue, 1-methyl-3-(2¹-aminopropyl)-4-hydroxy-indole, crystallizes from ethyl acetate in the form of druses having a melting point of 133—134°.

Keller's colour reaction: dark olive green.

Van Urk's colour reaction: green.

WHAT WE CLAIM IS:—

1. A process for the production of indole derivatives having the general formula XV shown in the accompanying diagrammatic drawings, in which R_1^1 designates an aralkyl group containing from 7 to 10 carbon atoms inclusive, R_2 designates a hydrogen atom or an alkyl group containing from 1 to 6 carbon atoms inclusive or an aralkyl group containing from 7 to 10 carbon atoms inclusive, each of R_3 and R_4 designates a hydrogen atom or an alkyl group containing from 1 to 6 carbon atoms inclusive, and A designates an alkylene group containing at most 3 carbon atoms, with the proviso that R_1^1 to R_4 need not be dissimilar, and with the further proviso that A and R_2 together must contain at least 2 carbon atoms when R_3 and R_4 each signify an alkyl group, which process is characterized in that an organic radical containing a nitrogen atom and

capable of being converted by a method involving reduction into an amino-containing group having the general formula XVI shown in the accompanying diagrammatic drawings, wherein A, R_1 and R_3 have the above meaning, is introduced into the 3-position of a compound having the general formula XIII shown in the accompanying diagrammatic drawings, wherein R_1' and R_2 have the above meaning, in known manner for substituting the 3-position of indoles and said organic radical is converted by a method involving reduction to said amino-containing group, said reduction being effected under conditions such that the group R_1' is not split off.

2. A process according to claim 1, characterized in that, when it is desired to produce a product wherein R_2 is a hydrogen atom, a compound of the general formula XIV shown in the accompanying diagrammatic drawings wherein R_1' has the meaning stated in claim 1, is reacted with an alkyl magnesium halide to give the corresponding substituted indole magnesium halide, the last mentioned material is reacted with a halogen carboxylic acid halide having the formula $X_1—CO—A—X_2$ wherein X_1 and X_2 represent each a halogen atom but need not be dissimilar, and A is as defined in claim 1, the resulting reaction product is treated with an amine having the general formula XVII shown in the accompanying diagrammatic drawings, wherein R_3 and R_4 have the significance stated in claim 1, and the resulting indolyl(3)-ketone having the general formula II shown in the accompanying diagrammatic drawings is reduced to give a compound of the general formula III shown in the accompanying diagrammatic drawings, said reduction being effected under conditions such that the group R_1' is not split off.

3. A process according to claim 1, characterized in that the end product of claim 2 is treated with an alkyl halide containing 1 to 6 carbon atoms or an aralkyl halide in the presence of an alkaline condensation agent so that a 1-substituted indole derivative results.

4. A process according to claim 1, characterized in that a compound of the general formula XIII shown in the accompanying diagrammatic drawings, wherein R_1' and R_2 have the significance stated in claim 1, is converted to the corresponding gramine compound by reaction with formaldehyde and a secondary amine, said gramine is quaternized and treated with an alkali metal cyanide to give an indolyl(3)-acetonitrile of the general formula IV shown in the accompanying diagrammatic drawings, the last mentioned material is saponified by an alkaline treatment to give the corresponding carboxylic acid, the last mentioned material is converted into the corresponding acid halide or azide, said halide or azide is treated with an amine having the general formula XVII defined in claim 2, and the resulting amide of the general formula V shown in the accompanying diagrammatic drawings, wherein R_1' R_2, R_3 and R_4 have the meaning stated in claim 1, is reduced under conditions such that the group R_1' is not split off, to give a compound having the general formula VI shown in the accompanying diagrammatic drawings, wherein R_1', R_2, R_3 and R_4 have the meaning stated in claim 1.

5. A modification of the process according to claim 4, characterized in that, when it is desired to produce an end product wherein A represents a methylene group and each of R_3 and R_4 represents a hydrogen atom, the said indolyl(3)-acetonitrile is reduced directly to give a compound having the general formula XVIII shown in the accompanying diagrammatic drawings wherein R_1' and R_2 have the meaning stated in claim 1, said reduction being effected under conditions such that the group R_1' is not split off.

6. A process according to claim 1, characterized in that, when it is desired to produce an end product wherein R_2, R_3 and R_4 represent each a hydrogen atom, a compound of the general formula XIV defined in claim 2 is converted by reaction with formaldehyde and a secondary amine to give the corresponding gramine having the general formula VIII shown in the accompanying diagrammatic drawings, wherein R_1' is as defined in claim 1, and R designates a dialkylamino group or a radical of a secondary cyclic amine, said gramine is treated with a nitroalkane of the general formula $H—A—NO_2$, wherein A is as defined in claim 1, in the presence of a proton acceptor, and the resulting nitro compound of the general formula IX shown in the accompanying diagrammatic drawings wherein R_1' and A are as defined above, is reduced to the corresponding amine of the general formula X shown in the accompanying diagrammatic drawings wherein R_1' and A are as defined above, said reduction being effected under conditions such that the group R_1' is not split off.

7. A process according to claim 1, characterized in that an indolyl(3)-aldehyde having the general formula XI shown in the accompanying diagrammatic drawings, wherein R_1' and R_2 have the meaning stated in claim 1, is heated in the presence of a condensation agent favouring the splitting off of water with a nitroalkane having the

formula H—A—NO_2, wherein A has the significance stated in claim 1, the resulting nitro compound having the general formula XII shown in the accompanying diagrammatic drawings wherein R_1' and R_2 have the above meaning and A^1 designates a group A less a hydrogen atom, is reduced to give a basic indole derivative of the general formula VII shown in the accompanying diagrammatic drawings wherein A, R_1' and R_2 have the above meaning, said reduction being effected under conditions such that the group R_1' is not split off.

8. A process for the production of compounds having the general formula I shown in the accompanying diagrammatic drawings, wherein R_1 designates a hydrogen atom only and R_2, R_3, R_4 and A are stated in claim 1 characterized in that an end product obtained in the process claimed in any one of the preceding claims is subjected to acid hydrolysis or reduction with hydrogen in the presence of a palladium catalyst or with an alkali metal in liquid ammonia.

9. A process for the production of compounds having the general formula I shown in the accompanying diagrammatic drawings wherein R_1 designates a hydrogen atom or an aralkyl group containing from 7 to 10 carbon atoms inclusive, and R_2, R_3, R_4 and A are as stated in claim 1, substantially as herein described with reference to any one of the Examples.

10. The compounds having the general formula I stated in claim 9 whenever produced by the process claimed in any one of the preceding claims.

11. The acid addition salts of the compounds claimed in the preceding claim.

12. A process for the production of the acid addition salts claimed in claim 11, which comprises salifying with an acid a compound having the general formula I stated in claim 9.

13. The compounds having the general formula I stated in claim 9 and their acid addition salts.

14. 4-Benzyloxy-3-(2'-dimethylamino-propyl)-indole.

15. 4-Hydroxy-3-(2'-dimethylamino-propyl)-indole.

16. 4-Benzyloxy-3-(3'-dimethylamino-propyl)-indole.

17. 4-Hydroxy-3-(3'-dimethylamino-propyl)-indole.

18. 1-Methyl-3-(2'-dimethylamino-ethyl)-4-benzyloxy-indole.

19. 3-(2'-Dimethylamino-ethyl)-4-benzyloxy-indole.

20. 1-Methyl-3-(2'-dimethylamino-ethyl)-4-hydroxy-indole and its oxalate (1 mol. of acid : 1 mol. of base).

21. 1-Benzyl-3-(2'-dimethylamino-ethyl)-4-benzyloxy-indole.

22. 1-Benzyl-3-(2'-dimethylamino-ethyl)-4-hydroxy-indole.

23. 1-Ethyl-3-(2'-dimethylamino-ethyl)-4-benzyloxy-indole.

24. 1-Ethyl-3-(2'-dimethylamino-ethyl)-4-hydroxy-indole.

25. 3-(2'-Methylamino-ethyl)-4-benzyloxy-indole.

26. 3-(2'-Methylamino-ethyl)-4-hydroxy-indole and its oxalate (2 mol. of base : 1 mol. of acid).

27. 3-(2'-Ethylamino-ethyl)-4-benzyloxy-indole.

28. 3-(2'-Ethylamino-ethyl)-4-hydroxy-indole and its oxalate (2 mol. of base : 1 mol. of acid).

29. 1-*n*-Butyl-3-(2'-aminoethyl)-4-hydroxy-indole and its oxalate (2 mol. of base : 1 mol. of acid).

30. 1-*n*-Butyl-3-(2'-aminoethyl)-4-benzyloxy-indole and its oxalate (1 mol of base : 1 mol. of acid).

31. 3-(2'-Aminopropyl)-4-benzyloxy-indole and its methanesulphonate.

32. 3-(2'-Aminopropyl)-4-hydroxy-indole and its maleate (1 mol. of base : 1 mol. of acid).

33. 1-Methyl-3-(2'-aminopropyl)-4-benzyloxy-indole.

34. 1-Methyl-3-(2'-aminopropyl)-4-hydroxy-indole.

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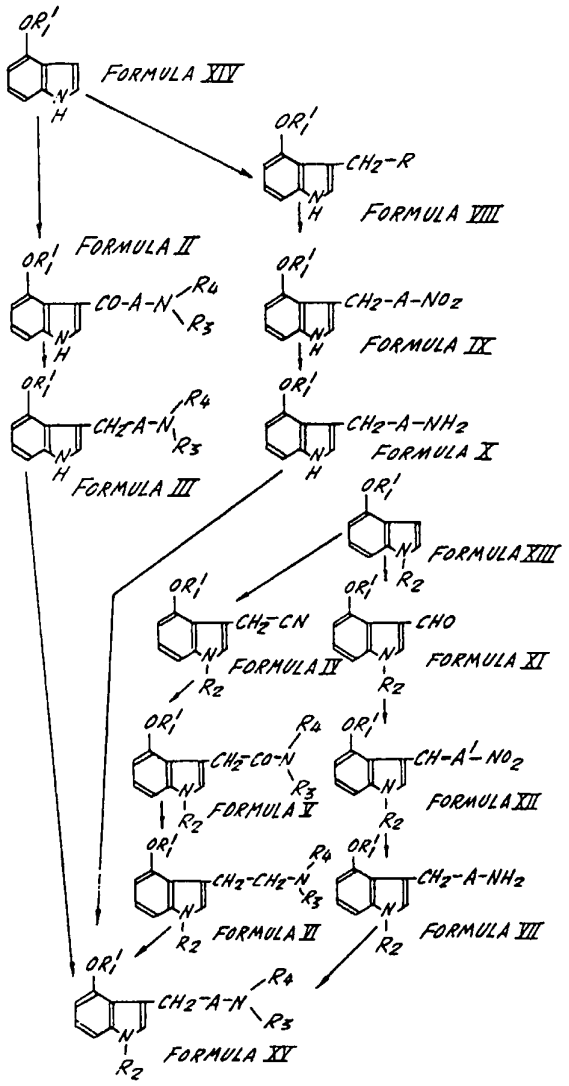

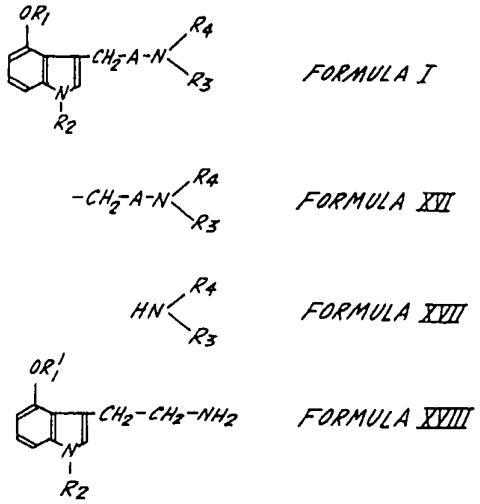

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